Articles

Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995

1913 to 1962: 2,056 Patients

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This is part I of a two-part article. See pages 88–97 for part II.

Splenomegaly was studied retrospectively at the University of California, San Francisco, School of Medicine, on all patients (N = 2,056) for the years 1913 to 1962. The patients were classified into several diagnostic groups, and these groups were tested for statistical significance (χ^2) with many clinical and laboratory variables to determine their predictive value. Hematologic disorders were associated with 57% of cases of splenomegaly and 81% of cases of massive splenomegaly. Among patients with splenomegaly, 19% had infectious diseases, 11% had hepatic diseases, and 9% had congestive or inflammatory disorders. The residual 4% were considered to have primary splenic disorders or a disorder of unknown cause. The commonest diseases associated with splenomegaly were hematologic (acute and chronic leukemias), infectious (malaria, endocarditis, and tuberculosis), hepatic (chronic liver disease), congestive (congestive heart failure), inflammatory (thyrotoxicosis), and other (cancers not metastatic to the spleen). The diseases most frequently associated with massive splenomegaly were the chronic leukemias. The disease with the highest incidence of massive splenomegaly was myelofibrosis (23 of 29 patients, 78%). Splenectomy was performed in 154 patients (7%), primarily for hematologic amelioration and hepatic hypersplenism. Hematologic diseases showed significant associations with lymphadenopathy, generalized lymphadenopathy, massive splenomegaly, and cytoses (P .001) and with progressive splenic enlargement ($P < .02$). Infectious diseases showed significant association with fever, and hepatic diseases showed significant association with abnormal results of liver function tests ($P < .001$). The findings of this retrospective study should be validated prospectively.

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The subject of splenomegaly in hospital-based patients from developed countries has elicited few published articles in the past 50 years or more. Splenomegaly is a diagnostic challenge because almost all the associated diseases are extrinsic to the spleen.[1] The various diseases associated with splenomegaly depend greatly on the geographic and clinical locale and perhaps even on the time of occurrence—for example, before or after the development of antibiotics.[2] The only general analyses of splenomegaly from a developed country were two office-based studies performed decades ago in which no diagnosis was established in more than 25% of patients.[3,4] Recent evaluations of splenomegaly come mostly from developing countries[2]; these reports emphasize infectious diseases or are focused on massive splenomegaly, especially its surgical aspects.[5] The only study of splenomegaly in hospital-based patients from a developed country, the United States, analyzed patients at a county hospital from 1983 to 1993.[6] Furthermore, the changing causes of splenomegaly extending back to before the antibiotic era from one clinical site have never previously been reported. This retrospective study of splenomegaly in hospital-based patients of a developed country from one university medical center over an 82-year period attempts to overcome many of these limitations.

The University of California, San Francisco, School of Medicine (UCSF) has retained all of its medical records since 1913, allowing a uniform study of all the

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ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
CHF = congestive heart failure
CLL = chronic lymphocytic leukemia
CML = chronic myelocytic leukemia
RBCs = erythrocytes [red blood cells]
UCSF = University of California, San Francisco
WBCs = leukocytes [white blood cells]

patients coded for splenomegaly over time. Those patients were retrospectively evaluated as the basis of this study. The various diseases found with splenomegaly were placed in diagnostic groups.[1] The association of these diagnostic groups with several clinical and laboratory features was analyzed for statistical significance to determine the diagnostic groups' predictive value.

Patients and Methods

Patient Demographics

All hospital records at UCSF for patients of any age diagnostically coded as splenomegaly from 1913 through 1962 were reviewed. *Splenomegaly* was defined as an enlarged spleen determined by one of the following: palpable on abdominal examination by at least two clinicians or noted on two written observations, more than 12 cm in length on a radiographic report, or greater than 250 grams wet weight of an excised spleen from an operation or autopsy. A total of 2,325 patients were coded with splenomegaly; 269 medical records (11.6%) of patients with splenomegaly could not be found. Therefore, the study was based on records of the remaining 2,056 patients. The incidence of splenomegaly in this study was 2,056 patients in about 220,000 admissions to UCSF, or 0.9%.

Clinical and Laboratory Features

The medical records were analyzed for the following clinical features: splenomegaly, massive splenomegaly, progressive splenic enlargement, hepatomegaly, lymphadenopathy, generalized lymphadenopathy, fever, and left upper quadrant pain and tenderness. *Hepatomegaly* was defined as a liver span of at least 12 cm in the right midclavicular line or any detection of the liver in the epigastrium. *Lymphadenopathy* was defined as enlarged lymph nodes detected during physical examination or imaging in at least two body sites and generalized lymphadenopathy if detected in more than two body sites. *Fever* was defined as a body temperature of greater than 38.0°C on two successive days. *Left upper quadrant pain or fullness* was defined as a patient's stated perception of pain or fullness in that area. *Left upper quadrant tenderness* was defined as the physician's perception of tenderness on palpation of that area or direct splenic tenderness. *Massive splenomegaly* was defined as a spleen palpable more than 15 cm below the left costal margin or below or at the level of the umbilicus during physical examination, or greater than 18 cm in length on a radiographic report, or more than 1,500 grams wet weight of an excised spleen from a surgical procedure or autopsy. In children, the weight of the spleen was normalized to a body weight of 70 kg (154 lb).

Patients' medical records were analyzed for the following laboratory features: cytopenia, such as thrombocytopenia and leukopenia, either alone or in combination; cytoses such as erythrocytosis, leukocytosis, or thrombocytosis, or a pronounced leftward shift of the neutrophilic leukocytes (WBCs) of the peripheral blood or the presence of nucleated erythrocytes (RBCs) on the peripheral blood smear, or a reticulocyte count of 0.10 (10% of RBCs) or greater than 200×10^9 per liter; and abnormal results on liver function tests. Anemia by itself was not evaluated as a cytopenia because of the high incidence of chronic anemia in hospital inpatients. A *pronounced leftward shift of the neutrophilic WBCs* was defined as myelocytes, promyelocytes, or myeloblasts on the peripheral blood smear. *Leukopenia* was defined as a WBC count of less than 4.0×10^9 per liter (4,000 per (l), thrombocytopenia as a platelet count of 120×10^9 per liter (120,000 per (l), leukocytosis as a WBC count of 15.0×10^9 per liter (15,000 per (l), thrombocytosis as platelet count of greater than 500×10^9 per liter (500,000 per (l), and erythrocytosis as a hematocrit of greater than 0.52 (52%). Stricter criteria were applied because mild degrees of leukopenia and thrombocytopenia are common in hospital inpatients. *Abnormal results of liver function tests* were defined by the presence of at least two of the following laboratory findings in a patient: an elevated total serum bilirubin level (>26 µmol per liter [>1.5 mg per dl]), an elevated serum alkaline phosphatase level (>1.5 times the upper limits of normal), or a decreased serum albumin value (<34 grams per liter [<3.4 grams per dl]). Other common tests of hepatic function that exist today were not available before 1937. For more recent patients, the following tests were usually available: an increased aspartate or alanine aminotransferase level (>2 times the upper limits of normal), a prolonged prothrombin time (>15 seconds), or a prolonged partial thromboplastin time (>35 seconds). When two or more disorders associated with splenomegaly existed in a patient, only the most likely disease was recorded.[4]

Diagnostic Classification and Statistical Analysis

The patients with splenomegaly were classified into several diagnostic groups: infectious diseases, hematologic disorder, hepatic disease, congestive or inflammatory disease, primary splenic disorder, and other. To determine the positive and negative associations of the clinical and laboratory features with the diagnostic groups, comparisons of these variables were made by χ^2 analysis. Differences at the .05 level were considered significant.

Results

A palpable spleen was regarded as splenomegaly; no patient was found in whom a left upper quadrant mass displaced a normal-sized spleen. Patients ranged in age from newborn to 87 years, with a median age of 34. Of the 2,056 patients, 23% were younger than 18 years,

TABLE 1.—*All Causes of Splenomegaly and Massive Splenomegaly by Diagnostic Group (N = 2,056)* *

Diagnostic Group	Total Splenomegaly, % 1913 to 1936 (n = 621)	Total Splenomegaly, % 1937 to 1962 (n = 1,435)	Subtotal With Massive Splenomegaly, % 1913 to 1936 (n = 118)	Subtotal With Massive Splenomegaly, % 1937 to 1962 (n = 334)	% of Each Diagnostic Group†
Hematologic	34	67	69	84	31
Infectious	43	8	17	3	8
Hepatic	10	11	8	9	17
Congestive or inflammatory	9	9	2	1	3
Other	2	2	1	0	2
Primary splenic	1	2	2	3	36
Unknown	1	1	1	0	5
Total	100	100	100	100	22

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of each diagnostic group indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

11% were younger than 2 years, 2% were older than 70 years, and 1% were older than 80 years. Sixty-one percent of the patients were male. All the patients were admitted to the hospital, which allowed the assignment to a diagnostic group of all but 21 patients (1%). Splenomegaly was detected by physical examination in 89% of the patients, by autopsy alone in 6%, and by radiographic examination alone in 5%.

Table 1 shows all the patients with splenomegaly and massive splenomegaly by diagnostic group. The commonest diagnostic group associated with splenomegaly in the earlier series was infectious diseases and in the later series was hematologic disorder. The commonest diagnostic group in both series associated with massive splenomegaly was hematologic disorder. The relative number of patients with hematologic disorder in the later series (67%) was almost double that of the earlier series (34%). The relative number of patients with infectious diseases in the later series (8%) was decreased more than fivefold compared to the earlier series (43%). Massive splenomegaly as a percentage of total splenomegaly for all disease groups collectively occurred in 22% of all the patients, 31% for all the patients with a hematologic disorder, and was highest (36%) for the patients with primary splenic disease.

Table 2 shows all the hematologic diseases in diagnostic detail. All the patients with hematologic malignancy (the leukemias plus lymphoma and polycythemia vera) accounted for 83% (968 of 1,170 patients) of those with splenomegaly and 85% (309 of 365 patients) of those with massive splenomegaly. The relative frequency of acute leukemia in the later series more than doubled,

TABLE 2.—*Hematologic Diseases Associated With Splenomegaly and Massive Splenomegaly* *

Diseases	Total Splenomegaly, % 1913 to 1936 (n = 214)	Total Splenomegaly, % 1937 to 1962 (n = 956)	Subtotal With Massive Splenomegaly, % 1913 to 1936 (n = 81)	Subtotal With Massive Splenomegaly, % 1937-1962) (n = 284)	% of Each Disease†
Lymphoma	24	4	23	5	37
CML	21	18	42	35	61
ALL/AML	16‡	36	10	20	17
Hemolytic anemia	13	11	14	7	23
Pernicious anemia	13	0.4	1	0	3
CLL	7	18	6	18	34
Polycythemia vera	4	9	2	7	23
Myelofibrosis	0	3	0	8	78
Other	2	0.4	0	0	0
Total	100	100	100	100	31

ALL = acute lymphoblastic leukemia, AML = acute myeloblastic leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelocytic leukemia

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine. Other includes 4 patients with aplastic anemia, 3 with idiopathic thrombocytopenic purpura, and 1 with multiple myeloma.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Acute leukemia often was not differentiated in the earlier series.

TABLE 3.—*Infectious Diseases Associated With Splenomegaly and Massive Splenomegaly* *

Diseases	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
	1913 to 1936 (n = 266)	1937 to 1962 (n = 119)	1913 to 1936 (n = 20)	1937 to 1962 (n = 9)	% of Each Disease†
Malaria	27	8	65	33	20
Endocarditis	21	13	5	11	3
Tuberculosis	12	16	5	0	2
Respiratory	8	16	0	0	0
Acute and chronic inflammatory‡	9	13	0	11	3
Syphilis	6	8	20	33	27
Peritonitis or UTI	0/3	10/0	0	0	0
Sepsis	4	7	0	0	0
Typhoid fever	5	0	5	0	7
Brucellosis or amebiasis	2/2	0	0	0	0
Infectious mononucleosis	0	8	0	11	11
Coccidioidomycosis or cryptococcosis	0	2	0	0	0
Total	100	100	100	100	8

UTI = urinary tract infections

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Acute infections include bacterial meningitis, acute prostatitis, acute skin infection, and enteric fever. Chronic infections include chronic pyelonephritis, chronic skin infections, pelvic inflammatory disease, chronic foot infections, purulent pericarditis, and febrile reversible hepatosplenomegaly of childhood.

16% to 36%; of chronic leukemias, increased slightly from 28% to 36%; and of myelofibrosis, increased more than 30-fold from less than 0.1% to 3%. The relative frequency of lymphoma decreased 6-fold from 24% to 4%, and that of pernicious anemia decreased more than 30-fold from 13% to 0.4%. Massive splenomegaly as a percentage of total splenomegaly occurred in 31% of the entire group of patients with a hematologic disorder: 78% with myelofibrosis, 61% with chronic myelocytic leukemia (CML), 37% with lymphoma, 17% with acute leukemia, and 3% with pernicious anemia.

Table 3 shows the infectious diseases in diagnostic detail. The commonest disease for the combined series associated with both splenomegaly and massive splenomegaly was malaria, which occurred in 82 patients. The second most common disease associated with splenomegaly was endocarditis and, with massive splenomegaly, was syphilis. Massive splenomegaly as a percentage of total splenomegaly occurred in 8% of all patients with infectious diseases, 27% with syphilis, 20% with malaria, 3% with endocarditis, and 2% with tuberculosis.

Table 4 shows the hepatic diseases in diagnostic detail. Patients with a stated diagnosis of Banti's disease or syndrome were classified as having chronic liver disease. The commonest disease associated with both splenomegaly (129 patients) and massive splenomegaly was chronic liver disease. Alcoholic liver disease was associated with 28% of the splenomegaly but only 10% of the massive splenomegaly. Massive splenomegaly as a percentage of total splenomegaly occurred in 17% of all patients with hepatic disease, 25% of patients with chronic liver disease, and 7% of patients with alcoholic liver disease. The relative frequency of portal vein thrombosis in the earlier series compared with the later series increased fourfold from 2% to 8% and for biliary cirrhosis, increased (0% to 6%) even more. The increase in diagnostic frequency of portal vein thrombosis and biliary cirrhosis may reflect improved diagnostic understanding and techniques.

Table 4 also shows the inflammatory diseases in diagnostic detail. The commonest cause of splenomegaly was thyrotoxicosis (25 patients) and of massive splenomegaly was collagen disease. The relative frequency of Felty's syndrome in the earlier series compared with the later series increased almost fivefold, from 5% to 24%, that of thyrotoxicosis decreased more than twofold from 46% to 19%, and that of rheumatic disease decreased even more from 23% to 0%.

Table 4 also shows the primary splenic diseases in diagnostic detail. The commonest disease associated with splenomegaly was cystic diseases (10 patients). The commonest diseases associated with massive splenomegaly were cystic diseases in 70% and storage diseases in 75% of these patients.

Congestive heart failure (CHF) was associated with splenomegaly in 16 patients in the early series and 95 patients in the later one. In 64 patients (67%) from the later series, the enlarged spleen was not palpable but rather was discovered usually at autopsy and occasionally on radiologic study. Several causes for the heart disease were found: atherosclerosis in 38%, congenital heart disease in 31%, rheumatic heart disease in 18%, cor pulmonale in 8%, and other heart diseases in 5%. A palpable spleen was associated with congenital heart disease in

TABLE 4.—*Hepatic, Inflammatory, and Primary Splenic Diseases Associated With Splenomegaly and Massive Splenomegaly* *

Diseases	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
	1913 to 1936	1937 to 1962	1913 to 1936	1937 to 1962	% of Each Disease†
Hepatic	(n = 63)	(n = 157)	(n = 10)	(n = 29)	
Chronic liver	52	58	80	79	25
Alcoholic liver	35	24	20	7	7
Portal vein thrombosis	2	8	0	7	14
VH/hepatoma	11/0	3/2	0/0	0/0	0/0
Biliary cirrhosis	0	6	0	7	22
Total	100	100	100	100	17
Inflammatory	(n = 39)	(n = 37)	(n = 4)	(n = 2)	
Thyrotoxicosis	46	19	0	0	0
Collagen	21	22	50	50	19
Felty's syndrome	5	24	25	0	9
Rheumatic	23	0	0	0	0
Pancreatitis/IBD	3/0	5/8	0	0	0
Amyloidosis	3	11	25	50	40
Sarcoidosis	0	11	0	0	0
Total	100	100	100	100	8
Primary splenic	(n = 4)	(n = 24)	(n = 1)	(n = 9)	
Cystic	50	33	100	67	70
SVT	0	25	0	0	0
Infarcts	25	12	0	0	0
Storage disease	0	16	0	33	75
Metastases	25	12	0	0	0
Total	100	100	100	100	36

IBD = inflammatory bowel disease, SVT = splenic vein thrombosis, VH = viral hepatitis

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

57% (17 of 30) of the patients, atherosclerosis in 26% (9 of 35), and rheumatic disease in 18% (3 of 17).

The spleen showed progressive enlargement during clinical observation in 88 patients: 9 in the earlier series and 79 in the later series. It showed a significant association ($P < .02$) with hematologic diseases (83%), especially the leukemias (Table 5). Progressive splenic enlargement also occurred in nonhematologic diseases: 5 had hepatic diseases, 4 had infectious diseases, 3 had primary splenic disease, and 3 had congestive or inflammatory disease.

Lymphadenopathy occurred in 40% of all the patients (Table 5) and was significantly associated ($P < .001$) with hematologic diseases. The individual lymphoproliferative diseases showed the highest incidence of patients with both lymphadenopathy and splenomegaly: lymphoma, 97% (96 of 99); chronic lymphoblastic leukemia (CLL), 80% (158 of 197); and acute lymphoblastic leukemia (ALL), 80% (151 of 188). Generalized lymphadenopathy occurred in 355 patients: 21 in the earlier series and 334 in the later one. Thus, generalized lymphadenopathy occurred in 43.0% (355 of 825) of the patients who had lymphadenopathy (Table 5) and was significantly associated ($P < .001$) with hematologic diseases. The lymphoproliferative diseases showed the highest incidence of generalized lymphadenopathy and splenomegaly: ALL, 57% (108 of 197); CLL, 55% (107 of 188); and lymphoma, 53% (52 of 99).

Percutaneous splenic puncture with a fine needle was performed in 16 patients of the combined series. A diagnosis was established in six of these patients: two had lymphoma, one had acute leukemia, one had CML, one had CLL, and one had subacute bacterial endocarditis. Most of the ten patients with normal findings were followed up with either a diagnostic splenectomy or an autopsy.

The 14 patients at UCSF with a friction rub heard over the spleen included 7 with infectious diseases (3 with endocarditis with splenic infarcts, 3 with disseminated tuberculosis, and 1 with infectious mononucleosis), 6 with hematologic malignancy (2 with CML, 2 with polycythemia vera, 1 with ALL, and 1 with CLL), and 1 patient with a large congenital splenic cyst. At the San Francisco General Hospital Medical Center, two patients had a splenic friction rub: one had disseminated tuberculosis, and the other had myelofibrosis with splenic infarct. Thus, 16 patients in all had a splenic friction rub: 10 with benign disease, and 6 with hematologic malignancy. Two patients had a splenic bruit: one had an arteriovenous malformation of the splenic blood vessels, and the other had CML and a simultaneous friction rub.

TABLE 5.—*Associations of Clinical and Laboratory Features With Diagnostic Groups of Splenomegaly (% of Patients)**

Diagnostic Group / *Features* / *Patients (N = 2,056), %*	*Hematologic* 57	*Infectious* 19	*Hepatic* 11	*Total* 100
Clinical				
Hepatomegaly (n = 1,368)	.61	18	13	67
Lymphadenopathy (n = 825)	.78†	11	3	40
General lymphadenopathy (n = 355)	.88†	7	2	17
Massive splenomegaly (n = 452)	.81†	6	9	22
Progressive splenic enlargement (n = 88)	.83‡	5	6	4
Fever (n = 383)	.29	52†	5	19
Laboratory				
Cytosis (n = 1,037)	.85†	10	3	50
Cytopenia (n = 675)	.57	9	13	33
Abnormal liver function (n = 144)	.9	4	78†	7

*Data are derived from the total number of patients at the University of California, San Francisco, School of Medicine (UCSF) for earlier series and later series at UCSF combined. The diagnostic groups of congestive and inflammatory diseases and primary splenic or other diseases have been omitted for lack of any associations.
†$P<.001$.
‡$P<.02$.

Four patients had splenic calcification: one each with echinococcal cyst, tuberculosis, hematoma, and lymphoma. Four patients had splenomegaly that disappeared under observation: two disappeared spontaneously (with 1 infectious mononucleosis, and a 5-year-old child with splenomegaly of unknown origin), and two disappeared after treatment (1 child with surgical ligation of a patent ductus arteriosus, and 1 adult with vigorous diuresis of CHF).

Table 5 shows the statistical positive associations of the clinical and laboratory features of splenomegaly with three of the diagnostic groups. Hematologic diseases showed a significantly positive association ($P < .001$) with lymphadenopathy, generalized lymphadenopathy, massive splenomegaly, and cytosis and a significantly positive association with progressive splenic enlargement ($P < .02$). Infectious diseases showed a significantly positive association ($P < .001$) with fever. Hepatic diseases showed a significantly positive association ($P < .001$) with abnormal results on liver function tests.

Discussion

Infectious Diseases

Malaria. From about 1830 to 1930, malaria was endemic in the San Joaquin Valley of California.[7] California enacted the Mosquito Abatement District Act in 1915, which was associated within a decade of a tenfold decline in the reported incidence of malaria.[8] The many isolated outbreaks of malaria in California in the past 50 years have been imported by US civilians and military personnel and foreign-born civilians. They provided the gametocytemic source for the autochthonous transmission of malaria by female anopheline mosquitoes.[9] The chances for the transmission of imported malaria in California, however, generally are exceedingly small because of the low probability that infected mosquitoes will survive beyond the 12 to 14 days of maturation time required for the plasmodia.[9] After fever, splenomegaly is the commonest physical finding still being reported for malaria.[10] Most of the patients with malaria were referred to UCSF from the San Joaquin Valley, were febrile at the time of diagnosis (>60%), and had a peripheral blood smear positive for plasmodia (>80%).

Endocarditis. The bacteriologic findings of the 72 patients with endocarditis in the combined series was *Streptococcus viridans* in 61, β-hemolytic streptococcus in 9, nonhemolytic streptococcus in 1, and *Salmonella typhosa* in 1. These data are similar to most series reported from before the introduction of antibiotics: as many as 95% of the reported patients were infected by the less virulent *S viridans.*[11] The 9 patients in this series with the more virulent β-hemolytic streptococcus all had a rapidly fatal acute endocarditis.[12] The rest of the patients with endocarditis had a more long-term course, which was historically called "subacute."[13] Only one patient at UCSF had a *Salmonella* species as the infecting organism, as gram-negative organisms rarely caused endocarditis even before the antibiotic era.[14] One adult patient with nonhemolytic streptococcal endocarditis had luetic heart disease, an association rarely reported.[15] Of 22 patients with splenic infarct, 18 (82%) had an embolic origin: 17 had patients had endocarditis and 1 had atrial fibrillation. In the other four patients, splenic infarcts were hematologic in origin (18%): three had leukemia, and one had polycythemia vera. In a more recent large study of splenic infarction, only 38% of splenic infarcts were embolic in origin, but 14% of patients required a splenectomy for persistent symptoms or complications.[16]

No patients with splenic infarction at UCSF required a splenectomy, but 14 of the 22 patients died and an autopsy was performed.

Most series have reported a low incidence of endocarditis in children in the first decade of life (<1% of patients), yet an incidence of 10% (7 of 72) of endocarditis and splenomegaly was found to occur in early childhood at UCSF.[17] In fact, one patient was only 19 days old, whereas the youngest reported child found in the literature was said to be 10 months old.[18] Three of the five children in this series had endocarditis associated with congenital heart disease.[19] The disappearance of rheumatic heart disease in this country and the introduction of antibiotics have led to a marked decline in endocarditis as a cause of splenomegaly, except in patients with congenital heart disease or prosthetic heart valves or who are injection-drug users.[20]

Tuberculosis. Of 51 patients with tuberculosis and splenomegaly, 27 (53%) were adults and 24 (47%) were children. All the children and all but four of the adults showed evidence of disseminated tuberculosis. In a large study of miliary tuberculosis in children, the incidence of splenomegaly was 54% (57 of 94).[21] Lymphadenopathy and splenomegaly occurred in 22 (44%) of the patients with tuberculosis at UCSF. Three of the adult patients with hepatosplenomegaly had leukopenia, which may have represented tuberculous hepatitis with hypersplenism.[22]

Syphilis. Of 26 patients with syphilis and splenomegaly, 20 were adult. All 6 children had hepatosplenomegaly with leukopenia or thrombocytopenia, which may have represented hypersplenism of luetic hepatitis. All six children, ages newborn to 12 years, were said to have congenital syphilis. Splenomegaly is the most consistent physical sign of congenital syphilis.[23] Five adult patients at UCSF had luetic hepatitis, and one had gummas of the spleen. Syphilis of the central nervous system occurred in five adults: two had tabes dorsalis, and two others had deficits of cranial nerves. Lymphadenopathy occurred in 8 (47%) of the 17 luetic patients, 3 of whom had generalized lymphadenopathy. Splenomegaly has been reported in several luetic conditions: congenital syphilis,[23] syphilitic hepatitis,[24] secondary or mucocutaneous syphilis,[25] tertiary syphilis of the central nervous system, and gummas.[26]

Typhoid fever. Of 14 patients with typhoid fever and splenomegaly, 9 were adults. All (100%) these patients had fever, and none of them had diarrhea. Eight (67%) of the 12 patients in whom a WBC count was performed had typical leukopenia. Others have reported thrombocytopenia as being more common[27] and leukopenia not to be a helpful diagnostic marker.[28] Splenomegaly was the leading clinical sign after fever and bradycardia.[29] Typhoid fever has virtually disappeared as a cause of splenomegaly, as evidenced by its absence in the later series (1937-1962) at UCSF. A recent report from Johns Hopkins University Hospital, Baltimore, Maryland, confirmed this pronounced reduction in splenomegaly since Osler's report in 1900.[29–31] In keeping with other reports of typhoid fever, all the patients in this series had nonspecific and mild manifestations of disease and a uniformly favorable outcome.[31]

Brucellosis. Of the six patients with brucellosis and splenomegaly, three worked at UCSF. Two of these patients were animal handlers, and the third was a laboratory technician who worked with *Brucella* species. A fourth patient was a sausage maker, the fifth was a student at the University of California, Davis, School of Veterinary Medicine, and the sixth had been recently vaccinated for brucellosis.[32] *Brucella* species is so infectious that it can be acquired in the laboratory merely from sniffing bacteriologic cultures containing the organism.[33] In the past decade, brucellosis in California has shifted from an occupational disease to a food-borne infection acquired in Mexico or from imported Mexican foods such as unpasteurized dairy products.[34]

Hematologic Diseases

Leukemia. The commonest hematologic disease associated with massive splenomegaly for the series was CML. It is one of few diseases that frequently presents with massive splenomegaly (in this series, 61%), rivaled by malaria, myelofibrosis, and kala azar.[35] Massive splenomegaly was twofold less in patients with acute leukemia than in those with CML. Leukocytosis also occurred less frequently in patients with acute leukemia than in those with CML. Among patients with acute leukemia, thrombocytopenia occurred in 51% (193 of 378) and leukopenia in 11% (42 of 378). In marked contrast, no patient on presentation with CML had either thrombocytopenia or leukopenia. Not surprisingly, neither myelofibrosis nor agnogenic myeloid metaplasia was reported in the earlier series. This series predated the description in 1937 of the disease.[36] It often was not then diagnostically distinguishable from leukemia[37] and, in fact, was often called "pseudoleukemia."[38]

A major question is, why did the incidence of all of the leukemias increase fourfold in the later series at a time when the incidence of lymphoma declined sixfold compared with the earlier series at UCSF? Chemotherapy for the leukemias was discovered in the 1940s and flourished at UCSF in the 1950s.[39] A federally funded chemotherapy center was established at UCSF by 1950, and later the Cancer Research Institute was formed. The presence of these units may have led to a notable increase in referrals from the medical community for innovative treatment of leukemia. At the same time, the treatment of lymphoma at the nearby Stanford University Medical Center, in San Francisco (now in Palo Alto, was vigorously pursued. These referral patterns for the later series would have led to more patients with leukemia at UCSF and more patients with lymphoma at Stanford University Medical Center than in the earlier series.

Pernicious anemia. There were 31 patients with pernicious anemia and splenomegaly. The diagnosis was established in several ways: achylia gastrica on gastric aspiration in 10 patients, the presence of combined system disease on neurologic or postmortem examination of the spinal cord in 7 patients, megaloblastic changes on the peripheral blood smear or bone marrow examination in 7 patients, macrocytosis and cytopenia in 4 patients, low

serum vitamin B_{12} concentrations in 2 patients, and the presence of generalized vitiligo in 1 patient. Generalized vitiligo and pernicious anemia are both autoimmune diseases with frequent association.[40] Leukopenia or thrombocytopenia occurred in 25 (88%) patients with pernicious anemia. Although the cytopenias have markedly declined since the beginning of specific therapy with vitamin B_{12} in 1926,[41] splenomegaly and cytopenias are still being reported in patients with pernicious anemia.[42]

Generalized Lymphadenopathy

There was a high incidence of generalized lymphadenopathy in the later series (23%) compared with the earlier series at UCSF (3%). Generalized lymphadenopathy was significantly associated ($P < .001$) with hematologic diseases. This finding is consistent with the dramatic increase of hematologic disease as the basis for the marked increase of generalized lymphadenopathy in this series. Similarly, the tenfold absolute and fourfold relative increase in the incidence of progressive splenic enlargement in this series with its significant association ($P < .02$) with hematologic diseases could have the same explanation. The lymphadenopathy in the combined series was generalized in 44% (355 of 825 patients), whereas a previous report found it in less than a quarter of their patients.[43] Hematologic diseases accounted for 88% of the generalized lymphadenopathy in this study, whereas a previous study reported that infectious diseases was associated with a majority of their patients with generalized lymphadenopathy.[44]

Inflammatory and Congestive Diseases

Congestive heart failure. All 16 patients with CHF and splenomegaly in the earlier series had underlying rheumatic heart disease. It is unclear why the incidence of CHF and splenomegaly in the later series had a fourfold increased incidence (95 patients) relative to the earlier series at UCSF, for an total incidence of 5.4% (111 of 2,056 patients). One explanation is that most of the patients with CHF in the later series had splenomegaly detected only at autopsy. In a study of splenomegaly performed in the United States in the 1950s, CHF was still the leading cause of splenomegaly.[4] In a similar study from India for the same period as at UCSF, the spleen in CHF was palpable in 54 of 690 patients or 7.8%.[45] In that study, the highest incidence of CHF and palpable splenomegaly in a specific heart disease was endocarditis in 57% of the patients, whereas those with rheumatic heart disease had splenomegaly detected in only 11%. At autopsy, the incidence of mild splenomegaly (>200 grams) was 48% and of moderate splenomegaly (>300 grams) was 22%.[45] Other series of CHF of that same period from the United States also report a greater than 10% incidence of moderate splenomegaly (>300 grams) in patients with CHF.[46,47] As in this series, the incidence of palpable splenomegaly in patients with CHF was a small fraction of that found at autopsy.[46] Congestive heart failure is now rarely associated with splenomegaly in developed countries, perhaps because of the extensive use of oral diuretics, the better care of cardiac patients, and the growing disappearance of rheumatic heart disease with the availability of antibiotics.[48]

Thyrotoxicosis. Of 25 adult patients with thyrotoxicosis and splenomegaly, 16 were women. Exophthalmos occurred in 17 of the patients, and a diffuse goiter was found in 15 patients. Graves' disease was present in 15 (60%) of the patients. In a large study of Graves' disease from the same period, a 33% incidence (44 of 132 patients) of splenomegaly reported.[49] In contrast, in a study from the United States for 1983 to 1993, Graves' disease was found in only 1 of 170 patients with splenomegaly.[6] Lymphadenopathy and splenomegaly at UCSF occurred in 8 (44%) of the 18 patients in the earlier series. There was a sixfold reduction of splenomegaly in hyperthyroidism from the earlier series (18 of 621 patients, or 2.9%) at UCSF compared with the later one (7 of 1,435 patients, or 0.5%). Severe and long-standing hyperthyroidism in the earlier period was associated with splenomegaly as a part of generalized lymphoid hyperplasia.[49] Today, splenomegaly and hyperthyroidism rarely occur.[50] Yet, the persistence of splenomegaly and lymphadenopathy in thyrotoxicosis may represent its imperfect treatment due to the lack of specific therapy for the underlying autoimmune disease.[51]

Felty's syndrome with rheumatoid arthritis, splenomegaly, leukopenia, and chronic infection occurred in 11 patients. The 2 patients who had splenectomies improved clinically.[52]

Splenic Puncture

Percutaneous splenic puncture with a fine needle was performed in 16 patients; a diagnosis was established in 5 (38%) of the patients with hematologic disease and 1 patient with subacute bacterial endocarditis. Aspiration biopsies with fine needles provide only cytologic examination,[53] whereas histologic confirmation with a tissue-core biopsy may be required.[54] All 16 splenic punctures in this series were performed "blind," before the introduction of guidance by imaging. This blind approach may have contributed to the rupture of the splenic vessels in one patient, which necessitated an emergency splenectomy.

Splenic Friction Rub

Sixteen patients had splenic friction rubs: eight with infectious diseases, six with hematologic malignancy, one with myelofibrosis, and one with primary splenic disease. At least three of the six patients with a hematologic disease and splenic friction rub had splenic infarcts. Osler noted in the 1906 edition of his textbook that on several occasions he had heard a peritoneal friction rub in patients with splenic infarcts,[55] an observation later confirmed by others.[56,57] One patient reported with a splenic abscess had a pleural friction rub that probably was related to the associated pleural disease.[58] A standard textbook on clinical diagnosis stated that splenic friction rubs were heard in patients with splenic infarction, neoplasia, and infections.[59] Splenic friction rubs were said to occur in patients with perisplenitis and with infarcts of the spleen of any source.[60] In that same report, two patients presented with splenic friction rubs: one had

chronic leukemia, and the other had subacute bacterial endocarditis.[60] Splenic friction rubs had been reported in patients with splenic infarcts and with chronic leukemia.[61]

Contrarily, most hepatic friction rubs are associated with malignancy, usually solid tumors that are metastatic to the liver.[62] Systolic arterial murmurs or bruits over the liver or adjacent chest were found in hepatomas because they are very vascular tumors.[63]

Vascular murmurs or splenic bruits were heard over greatly enlarged spleens in patients with benign diseases or with hematologic malignancy[64] and were said to result from increased blood flow of the greatly enlarged organ.[56] The one patient in this series with an arteriovenous malformation of the splenic blood vessels had a splenic bruit. Thus, the sounds heard in patients at UCSF over enlarged spleens of benign diseases and several hematologic cancers were all said to be friction rubs that should have been synchronous with respiration, whereas the sounds (bruits) reported over greatly enlarged spleens were demonstrated by phonocardiography to be vascular murmurs synchronous with the pulse.[56]

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